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(19)

(54) PHARMACEUTICAL COMPOSITIONS CONTAINING ANTHOCYANIDINES

(71) We, INVERNI DELLA BEFFA S.p.A., an Italian Company of Via Ripamonti, 99, Milan, Italy, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:

This invention relates to pharmaceutical compositions and processes for their preparation.

Anthocyanidines are a group of known polyphenolic substances. These products, as well as being preparable by total chemical synthesis, may be obtained by hydrolysis of their glycosides which are widely distributed in nature. These glycosides, and particularly the glucosides, are known as anthocyanins and are present in the fruits of the bilberry, vine, elder, currant, bramble and raspberry.

We have now found that anthocyanidines are endowed with remarkable cicatrising and epithelium-regenerating properties which render them particularly useful in the treatment of cutaneous wounds, torpid sores, and external and internal ulcers. Also anthocyanidines have been found to possess distinct anti-inflammatory, vaso-protective, hypolipaemic, hypocholesterolaemic and hypoglycaemic activities.

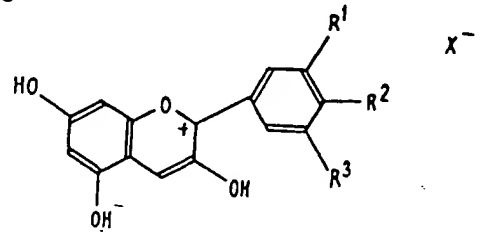
Anthocyanidines frequently have extremely low toxicities which renders them particularly useful for prolonged treatments.

Clinically, the substances may be administered singly or in the form of mixtures with one another, in the pure state or in the form of crude or partially purified extracts, for example extracts of the crude product obtained by hydrolysis of naturally-occurring mixtures of anthocyanins. Preferably at least a portion of extracted materials other than the anthocyanidines are eliminated from the extracts.

Thus according to the present invention there are provided pharmaceutical compositions comprising in admixture with a pharmaceutically acceptable diluent or carrier, an anthocyanidine, or a pharmaceutically acceptable salt thereof, with the proviso that when the sole diluent or carrier is a liquid solvent, the composition is sterile and pyrogen-free.

Preferably, since they may be obtained readily by hydrolysis of glycosides contained in common fruit and also on account of their pronounced pharmaceutical activity, the active constituent or constituents contained in the pharmaceutical compositions of the invention are cyanidine, peonidine, delphinidine, petunidine, pelargonidine or malvidine.

These anthocyanidines, which may be in the form of salts with any pharmaceutically acceptable anion (e.g. chloride, sulphate, phosphate, acetate or hydroxyl), may be represented by the following formula:



wherein: $R^1 = R^2 = -OH$ and $R^3 = H$ (cyanidine)
$R^1 = -OMe$, $R^2 = -OH$ and $R^3 = H$ (peonidine)
$R^1 = R^2 = R^3 = OH$ (delphinidine)

R^1 = OMe and R^2 = R^3 = OH (petunidine)
R^1 = R^3 = -OMe and R^2 = -OH (malvidine)
R^2 = -OH and R^1 = R^3 = H (pelargonidine)
and X- is the pharmaceutically acceptable anion.

The particular galenic form of the compositions of the invention depends on the intended route of administration and the condition to be treated and such forms may be amorphous or in the form of shaped dosage units. Examples include sterile liquids suitable for parenteral administration, forms suitable for oral administration (e.g. tablets, capsules, solutions or suspensions); forms suitable for insertion into a body cavity (e.g. anal or vaginal suppositories); forms suitable for topical administration (e.g. ointments, creams, gels and aqueous solutions or suspensions) and dentifrices.

In formulating compositions according to the invention, a wide range of excipients may be used, the nature of which will depend, of course, on the intended mode of application of the composition. Examples include preservatives and buffering, thickening, suspending, stabilising, wetting, emulsifying, colouring and flavoring agents and in particular carboxy vinyl polymers, propylene glycol, ethyl alcohol, water, cetyl alcohol, saturated vegetable triglycerides, fatty acid esters or propylene glycol, triethanolamine, glycerol, starch, sorbitol, bentonite, carboxymethyl cellulose, laurylsulphate, dicalcium phosphate, powdered silica and lecithin.

Frequently, more than one diluent or carrier is advantageously used.

The compositions of the invention have been found to be particularly useful in the treatment of wounds, gastric and duodenal ulcers, inflammatory conditions of the mouth and throat, pathogenic conditions of the vascular system and disorders caused by impaired lipidic and glycidic metabolism.

This invention also includes a process for producing the compositions defined above which comprises extracting an anthocyanin from plant tissue, hydrolysing the anthocyanin to form an anthocyanidine, purifying the anthocyanidine and admixing the purified anthocyanidine in free form or in the form of a pharmaceutically acceptable salt with a pharmaceutically acceptable excipient.

The invention also provides a method of inducing a cicatrising, epithelium - regenerating, anti-inflammatory, vaso-protective, hypolipaemic, hypocholesterolaemic or hypoglycaemic response in a non-human subject, which comprises administering to the subject a dose of an anthocyanidine in an amount sufficient to produce the required response.

The compositions according to the invention preferably contain at least 0.2% and most preferably at least 0.5% by weight of anthocyanidines. More concentrated compositions are preferred for internal (i.e. enteral or parenteral) administration, particularly those containing at least 1% and more particularly at least 5% by weight of anthocyanidines. The compositions may be administered at a daily dosage rate of from 1 to 100 mg/kg, preferably 5 to 50 mg/kg of anthocyanidines.

The following experimental data illustrates the pharmacological properties of anthocyanidines:

I. *Anti-ulcer activity - Shay's ulcer in the rat*

In Shay's ulcer in the rat, the oral administration of bilberry anthocyanidines at doses of 25 to 50 mg/kg five times, at 48, 33, 22 and 9 hours prior to the ligature of the pylorus and 1 hour after the operation, was found to diminish the ulcer index observed with the controls, by 28 and 39 per cent respectively. (See Table 1).

Table 1 - Anti-ulcer activity - Shay's gastric ulcer in the rat

TREATMENT	*Dose mg/kg (1)*	*Number of animals*	*Number of ulcers of each class (2)*					*Ulcer Index*	*Variation of Ulcer Index (3)*	*Number non-ulcerated stomachs*
			I	*II*	*III*	*IV*	*V*			
Controls (water)	-	19	295(295)	44(220)	15(150)	2(40)	17(340)	55	-	-
Bilberrry anthocyanidines	25	18	100(100)	20(100)	13(130)	9(180)	10(200)	39.5	-28	11
	50	18	271(271)	21(105)	7(70)	3(60)	5(100)	33.6	-39	5

(1) Doses administered orally 5 times, 48, 33, 22 and 9 hours prior to ligature of the pylorus and 1 hour after

(2) In parentheses, the product of the number of the ulcers and the value of the individual classes according to the evaluation criterion of Keyriläinen T.O. and Passonen M.K. (Acta Pharmacol. et Toxicol. *13*, 22, 1957)

(3) Percentage reduction compared with controls

II. *Activity upon lipidic metabolism*

1) *Hyperlipaemia induced by olive oil*

Hyperlipaemia was induced by orally administering olive oil to male Sprague-Dawley rats of mean weight of 165 g. which had been fasted for 16 hours. The administration of olive oil was effected 3 hours prior to sacrifice, at a dose of 2 ml/gk orally.

Bilberry anthocyanidines and cyanidine obtained from elder fruit were administered intraperitoneally 1 hour prior to the administration of the olive oil in equal strength doses dissolved in 0.5 ml/kg of physiological solution. Table 2 shows that the bilberry anthocyanidines significantly diminish the free fatty acids and the triglycerides respectively by 36.60 and 86% in comparison with the controls, and that the cyanidine obtained from elder diminishes the free fatty acids and the triglycerides respectively by 32.70 and 67.90%, again in comparison with the controls.

2) *Hyperlipaemia induced by Triton WR 1339*

Hyperlipaemia was induced by intravenous administration of 225 mg/kg, 0.5 ml/kg of Triton WR 1339 dissolved in physiological solution, in male Sprague-Dawley rats of mean weight 210 g. which had been fasted for 24 hours, 8 hours prior to sacrifice ("Triton" is a Registered Trade Mark)

The substances under test were injected intraperitoneally twice: the first administration simultaneously with the Triton and the second 4 hours later, in equal-strength doses dissolved in 0.5 ml/kg of physiological solution.

From Table 3 it can be seen that bilberry anthocyanidines significiantly diminish the plasma triglycerides and cholesterol respectively to 29.56 and 16.03% in comparison with the controls and that elder cyanidine diminishes these lipids by 23.65 and 16.67% respectively, again in comparison with the controls.

Table 2 - Effect upon hyperlipaemia induced by olive oil

TREATMENT	Dose mg/kg	Number of animals	NEFA* $\mu Eq/l$	Triglycerides mg/100ml
A Controls	-	16	1013.22±44.30	384.52±42.34
B 58% anthocyanidines from bilberry	43.1	16	642.33±27.44° (-36.60)	53.73±6.24° (-86.00)
C 32% cyanidine from elder	72.12	16	681.73±25.21° (-32.70)	123.62±36.68° (-67.90)

* Non-esterified fatty acids

° Significantly different ($p<0.001$) from the mean obtained from group A according to Student's "t" test

Note: In parentheses, the percentage difference from the controls.

Table 3 - Effect upon hyperlipaemia induced by Triton WR 1339

TREATMENT	Dose mg/kg	Number of animals	Triglycerides mg/100ml	Total cholesterol mg/100ml
A Controls	-	8	621.56±36.87	189.93±11.76
B 58% Anthocyanidines from bilberry	21.5 x 2	8	437.85±26.01°° (-29.56)	159.50±3.20° (-16.03)
C 32% cyanidine from elder	36.6 x 2	8	474.59±38.06° (-23.65)	158.28±6.58° (-16.67)

° Significantly different ($p<0.05$) from the mean obtained with the controls according to Student's "t" test

°° Significantly different ($p<0.01$) from the mean obtained with the controls according to Student's "t" test

Note: In parentheses the percentage difference from the controls

III. *Activity upon capillary permeability*

The action upon capillary permeability was studied on Sprague-Dawley rats of mean weight of 220 g. which had been fasted 18 hours prior to the experiment according to the method of Ankier and West; Brit. J. Pharmacol. *33*, 304, 1968. From Table 4 it can be seen that bilberry anthocyanidines administered experimentally by intraperitoneal route at doses of 9, 18 and 36 mg/kg give a significant diminution of the capillary permeability respectively by 12; 25.2 and 55.4% in comparison with the controls.

Table 5 shows the experimental data obtained by oral treatment with bilberry anthocyanidines. The produce was administered experimentally in two doses and specifically at 36 and 72 mg/kg, and gave a significant inhibition of the capillary permeability of 24.6 and 44.4% in comparison with controls.

Table 4 - Capillary permeability induced by bradykinin in the rat

TREATMENT mg/kg		Evans Blue μg	Inhibition per cent
Controls 0.9% NaCl	0.5 ml/hg	16.87±0.20	-
70% anthocyanidines from bilberry	9		12
	18	12.63±0.10°	25.2
	36	7.54±0.30°	55.4

Note: Bradykinin 2μg/0.1 ml injected intradermally at 3 points into the depilated abdominal zone of each rat

Treatment with the substances under examination 30 minutes prior to the bradykinin

Sacrifice 30 minutes after the bradykinin

o Significantly different ($p<0.01$) from the mean obtained with the controls according to Student's "t" test

Table 5 - Capillary permeability induced by bradykinin in the rat

TREATMENT mg/kg		Evans Blue μg	Inhibition per cent
Controls (H_2O)	1 ml/hg	15.50±0.54	-
70% anthocyanidines from bilberry	36	11.70±0.51°	24.6
	72	8.60±0.58°	44.4

Note: Bradykinin 2 μg/0.1 ml injected intradermally at 3 points of the depilated abdominal zone of each rat

Treatment with the substances under examination 60 minutes prior to the bradykinin

Sacrifice 30 minutes after the bradykinin

o Significantly different ($p<0.01$) from the mean obtained with the controls according to Student's "t" test

Activity upon capillary resistance

The capillary resistance was studied in rats subjected to deficiency diet according to the method of Charlier R. et al; Arch. intern. Physiol. Biochem., *71*, 1, 1963.

Table 6 shows that the bilberry anthocyanidines used experimentally in two doses by oral route increased the capillary resistance with time and in significant manner.

Table 6 - Activity upon the capillary resistance of rats subjected to dietary deficiency

TREATMENT mg/kg/os		Time from treatment hours 0	2	4	6
70% anthocyanidines from bilberry	36	15.5±0.32	17.0±0.32°	17.2±0.14°	17.2±0.14°
	72	15.5±0.32	17.3±0.41°	17.6±0.41°	17.6±0.41°

° Significantly different from the time 0 ($p<0.05$) according to Student's "t" test for non-independent samples

Table 7 - Effect upon hyperlipaemia induced by olive oil

TREATMENT		Dose	Number of Animals	NEFA* $\mu Eq/l$	Triglycerides
A	Controls (NaCl 0.9%)	1ml/hg	8	1056.5 ± 29.3	312.8 ± 33.6
B	Pelargonidine chloride	100mg/kg	8	671.5 ± 27.4 (-36.4)°	140.4 ± 11.6 (-55.1)°
C	Peonidine	100mg/kg	8	950.5 ± 22.9 (-10.0)	176.0 ± 21.3 (-43.8)°

* Non-esterified fatty acids.

° Significantly different ($p<0.05$) from the mean obtained from group A to Student's "t" test.

Note: In parentheses, the percentage difference from the controls.

The anthocyanidines suitable for the preparation of the composition according to the invention may be obtained by hydrolysis of anthocyanins contained in plant extracts or by synthetic methods. Generally, plants containing anthocyanins are extracted with alcoholic solvents (particularly low alkanols containing 1 to 4 carbon atoms) containing small quantities of mineral acids which stablise the pyran form of the anthocyanic nucleus.

The warming of the extract with acid causes hydrolysis of the glycoside residue of the anthocyanins thus forming anthocyanidines which may be incorporated into the compositions of the invention either as mixtures of after having being isolated as pure products using column chromatography.

Examples 1 and 2 below describe the preparation of anthocyanidine from elder fruits and of mixtures of five anthocyanidines (malvidine, delphinidine, cyanidine, peonidine and petunidine) from a methanol extract of bilberry fruits.

By synthetic methods flavones (L. Bauer, Chem. and Ind. 433, 1954 and H.G.C. King, J. Chem. Soc. 901, 1957), catechins (J. Savollary, Compt. Rend. 217, 86, 1943 and H. Apple J. Chem. Soc. 426, 1935) and oligomers of catechins (T.A. Geissman and H.F.K. Dittmar, Phytochemistry 4, 359, 1965) may be transformed into anthocyanidines.

Besides, it is possible to obtain anthocyanidines by condensing 2,4,6-trihydroxybenzaldehyde 2-0-benzoate and an omega-acetoxy-acetophenone suitably substituted in the aromatic nucleus according to the methods of R. Robinson (A. Robertson and R. Robertson, J. Chem. Soc. 1526, 1928 A. Robertson, R. Robinson and J. Sugiura, J. Chem. Soc. 1533, 1928 S. Murakami and R. Robinson, J. Chem. Soc. 1537, 1928 W. Bradley and R. Robertson J. Chem. Soc. 1541, 1928). Example 3 describes the synthesis of pelargonidine chloride.

Example 1 -*Preparation of anthocyanidines from elder anthocyanins*

(A) *Extraction from elder*

13.5 kg of fresh ripe elder fruits were extracted at room temperature with anhydrous methanol containing 1% of hydrochloric acid. The extracts were concentrated *in vacuo* to small volume and an aqueous solution of 30% of neutral lead acetate added with agitation. An abundant precipitate was obtained which was filtered and washed with water. 200 g. of crude lead salts were obtained which were then suspended with agitation in 600 ml of anhydrous methanol containing hydrochloric acid, agitated at room temperature and the insoluble material elminated by filtration.

The methanolic solution was then concentrated *in vacuo* at low temperature to small volume and subsequently poured with agitation in to ether. The precipitate was filtered and dried *in vacuo* at room temperature. 30 g. of glucosides were obtained, equivalent to 15% cyanidine.

(B) *Formation of crude cyanidine*

30 g. of glucosides equivalent to 15% cyanidine were dissolved in a mixture constituted by methanol and concentrated hydrochloric acid in the ratio 8 : 2. Heating was effected under reflux for 3 hours. The solution was then diluted wih water and concentrated *in vacuo* until complete elimination of the methanol. A precipitate was obtained which was filtered and washed with water. After drying, 6 g. of crude hydrolysate was obtained containing 20% cyanidine.

(C) *Purification of the cyanidine*

The crude 20% cyanidine was purified by chromatography on Sephadex LH 20, eluting with 95% ethanol containing 1% of concentrated hydrochloric acid. ("Sephadex" is a Registered Trade Mark)

Although anthocyanidines for incorporation in pharmaceutical compositions according to the invention are most conveniently prepared by hydrolysis of fruit anthocyanins (anthocyanosides), for example as described above, they may also be obtained synthetically by reduction of quercetin and its derivatives or rutin (L. Bauer, Chem. and Ind. 1954, 433-4; H.G.C. King, J. Chem. Soc. 1957, 3901-3). Other methods reported in literature enable cyanidine to be obtained from epicatechin pentaacetate (A.K. Ganguli et altri Proc. Indian Aca. Sci, 46A, 25-8, 1957) and from catechin and its derivatives (J. Lavollary, Compt. Rend. *217*, 86-8, 1943; H. Apple J. Chem. Soc. 1935, 426-9).

Moreover cyanidine can be obtained by acid hydrolysis of oligomers (polymers of low molecular weight, generally dimers) of catechins (T.A. Geissman and H.F.K. Dittmar Phytochemistry, 1965, vol. 4 pp 359-368).

Example 2 -*Preparation of anthocyanidines from bilberry*

Using the procedure used in Example 1, an extract was obtained rich in anthocyanosides equivalent to not less than 25% in total anthocyanidines (malvidine, delphinidine, cyanidine, peonidine and petunidine).

Subsequently the extract was hydrolysed and the anthocyanidines are purified by the following procedure:

The anthocyanosides were dissolved in a mixture of methanol and concentrated hydrochloric acid in the ratio 8 : 2, and hydrolysed by means of boiling under reflux for 3 hours. The precipitate formed was cooled and filtered. The liquid was then concentrated *in vacuo* to eliminate all the methanol, and four extractions with isoamyl alcohol were effected on the concentrate. The reunited isoamyl extracts were concentrated *in vacuo* and precipitated with agitation in ethyl ether. After filtration and drying, anthocyanidines at 50 - 60 per cent were obtained.

Example 3 Synthesis of Pelargonidine Chloride

24g of 2,4,6-trihydroxybenzaldehyde 2-0-benzoate were dissolved by warming in 500ml of ethyl acetate and 20g of p-hydroxyacetoxyacetophenone added. Gaseous hydrochloric acid was introduced to saturation and the mixture kept at room temperature overnight. The obtained solid was then dissolved in 3 litres of methanol, 150 ml of conc. aqueous HCl added and the mixture boiled under reflux for 6 hours. The product was then evaporated under vacuum to 250 ml and allowed to crystallise at 4°C. Yield 14 g of pelargonidine chloride.

Pharmaceutical compositions according to the invention was prepared in accordance with the following formulations:

Injectable solution for freeze-drying

Bilberry anthocyanidines (50% by weight)	25 mg
Excipients (mannite, sodium chloride, sodium ethylene diamino tetraacetate, thiourea) q.s. to	125 mg
Solvent: double-distilled water (pyrogen-free)	3 ml

Capsules

Grade anthocyanidines (25% by weight)	100 mg
Excipients (mannite, citric acid, sodium chloride, thiourea, sodium ethylene diamino tetraacetate, lactose, methyl cellulose, magnesium stearate) q.s. to	200 mg

(The components were mixed together and then filled into capsules.

Capsules

Elder anthocyanidines (containing 20% cyanidine)	125 mg
Excipients (mannite, citric acid, sodium chloride, thiourea, sodium ethylene diamino tetraacetate, lactose, methyl cellulose, magnesium stearate) q.s. to	250 mg

(The components were mixed together and then filled into capsules)

Injectable solution for freeze-drying

Cyanidine	15 mg
Excipients (mannite, sodium chloride, sodium ethylene diamino tetraacetate, thiourea) q.s. to	125 mg
Solvent: double-distilled water (pyrogen-free)	3 ml

Tablets

Grape anthocyanidines (60% by weight)	35 mg
Excipients (maize starch, lactose, citirc acid, magnesium stearate, thiourea, sugar, talc, gum arabic, magnesium carbonate) q.s. to	200 mg

Ointment

Bilberry anthocyanidines (50% by weight)	0.5 g
Excipients (cetyl alcohol, saturated vegetable triglycerides, esters of polyethylene glycol 2000 with fatty acids C_{12}-C_{14}, Tween 80, para-oxy benzoates, sorbitol, carboxy vinyl polymer, sodium sulphite, triethanolamine, lecithin, purified water, lactic acid) q.s. to	100 g

Ointment

Elder anthocyanidines (containing 20% cyanidine)	1 g
Excipients (cetyl alcohol, saturated vegetable triglycerides, esters of polyethylene glycol 2000 with fatty acids C_{12}-C_{14}, Tween 80, para-oxybenzoates, sorbitol, carboxyvinyl polymer, sodium sulphite, triethanolamine, lecithin, purified water, lactic acid) q.s. to	100 g

Dentrifice gel

Bilberry anthocyanidines (35% by weight)	0.5 g
Excipients (carboxyvinyl polymer, sorbitol, propylene glycol, sodium sulphite, ethyl alcohol, para-oxy benzoates, sodium lauryl sulphate) q.s. to	100 g

Dentifrice paste

Grape anthocyanidines (60% by weight)	0.5 g
Excipients (citric acid, sodium bisulphite, sorbitol, ammonium glycyrrhizinate, maize starch, glycerine, para-oxy benzoates, titanium dioxide, calcium phosphate, sodium lauryl sulphate, flavourings, purified water) q.s. to	100 g

(Conventional techniques were used to prepare the tablet, ointment and dentifrice formulations from the ingredients specified).

WHAT WE CLAIM IS:-

1. A pharmaceutical composition comprising a pharmaceutically acceptable excipient and as active ingredient an anthocyanidine or a pharmaceutically acceptable salt thereof, with the proviso that where the sole excipient is a liquid solvent, the composition is sterile and pyrogen-free.
2. A composition according to Claim 1 containing a preservative or a buffering, thickening, suspending, stablizing, wetting, emulsifying, colouring or flavouring agent.
3. A composition according to Claim 1 or Claim 2 comprising excipient selected from carboxy vinyl polymers, propylene glycol, ethyl alcohol, water, cetyl alcohol, saturated vegetable triglycerides, fatty acid esters, propylene glycol, triethanolamine, glycerol, starch, sorbitol, bentonite, carboxymethyl cellulose, laurylsulphate, dicalcium phosphate, powdered silica and lecithin.
4. A composition according to any preceding claim comprising at least two excipients.
5. A composition according to any preceding claim in which the anthocyanidine is

selected from cyanidine, peonidine, delphinidine, petunidine, malvidine and pelargonidine.

6. A composition according to any preceding claim in a form suitable for parenteral administration.

7. A composition according to any one of Claims 1 to 5 in a form suitable for oral administration.

8. A composition according to any one of Claims 1 to 5 in the form of a suppository.

9. A composition according to any one of Claims 1 to 5 in the form suitable for topical administration.

10. A composition according to any one of Claims 1 to 5 in the form of a dentifrice.

11. A composition according to any one of Claims 1 to 5 in the form of a dosage unit.

12. A composition according to any one of Claims 1 to 11 containing at least 0.2 wt % of anthocyanidines.

13. A composition according to Claim 12 containing from 1 to 50 wt.% of anthocyanidines.

14. A composition according to Claim 13 containing at least 5 wt.% of anthocyanidines.

15. A process for producing a pharmaceutical composition as claimed in any preceding claim which comprises extracting an anthocyanin from plant tissue, hydrolysing the anthocyanin to form an anthocyanidine, purifying the anthocyanidine and admixing the purified anthocyanidine in free form or in the form of a pharmaceutically acceptable salt with a pharmaceutically acceptable excipient.

16. A method of producing a cicatrising, epithelium - regenerating, anti-inflammatory, vaso-protective, hypolipaemic, hypocholesterolaemic or hypoglycaemic response in a non-human subject, which comprises administering to the subject dose of an anthocyanidine in an amount sufficient to produce the required response.

17. A method according to Claim 16 in which the anthocyanidine is selected from cyanidine, peonidine, delphinidine, petunidine, malvidine and pelargonidine.

18. A method according to Claim 16 in which the anthocyanidine is administered in the form of a composition as claimed in any one of Claims 1 to 14.

19. A method according to Claim 16 in which the anthocyanidine is administered in the form of a composition produced by a process as claimed in Claim 15.

20. A method according to any one of Claims 16 to 19 in which the anthocyanidine is administered to an animal afflicted with wounds, gastric and duodenal ulcers, inflammatory conditions of the mouth and throat, pathogenic conditions of the vascular system or disorders caused by impairment of lipidic or glycidic metabolism.

21. A method according to any one of Claims 16 to 20 in which said effective dose is from 1 to 100 mg/kg per day of anthocyanidines.

22. A method according to claim 21 in which said effective daily dose is from 5 to 50 mg/kg per day of anthocyanidines.

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